No. 40.

THE CONSTITUTION OF CHRYSOPHANIC ACID AND OF EMODIN

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THE WELLCOME CHEMICAL RESEARCH LABORATORIES

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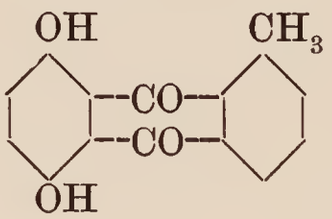
CXXVII.—*The Constitution of Chrysophanic Acid and of Emodin.*

By Hooper Albert Dickinson Jowett and Charles Etty Potter.

Although chrysophanic acid and emodin have long been known to be respectively the di- and tri-hydroxy-derivatives of a methylanthraquinone, the position of the substituting groups has remained undetermined. The exact constitution of these substances is, however, of considerable importance from a pharmacological standpoint, inasmuch as they occur naturally in several drugs possessing a cathartic action. Hesse (*Annalen*, 1899, **309**, 32) has suggested certain formulæ for these substances, but he adduces no evidence, either theoretical or experimental, in support of his assumptions. The object of this investigation was to determine the position of the substituting groups, and, if possible, to synthesise the substances themselves. Although we have failed to accomplish these syntheses we are able, with a considerable degree of certainty, to propose formulæ for both these compounds.

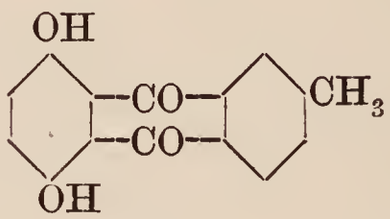
Chrysophanic acid yields, on distillation with zinc dust, a product which Liebermann (*Annalen*, 1876, **183**, 159) considered to be 2-methylanthracene, but owing to the great similarity which exists between the isomeric methylanthracenes this point cannot be considered as being definitely proved. Chrysophanic acid was not methylated, even when treated with excess of sodium and methyl iodide in methyl alcohol at 100° (Jowett and Potter, Trans., 1902, **81**, 1584). It

follows that both hydroxyls must be contiguous to a carbonyl group in the anthraquinone molecule. Furthermore, by fusion with caustic alkali or by oxidation with permanganate, it does not yield any derivative of benzoic acid, but gives rise only to simple oxidation products such as oxalic acid, from which it may be concluded that the hydroxyl groups are attached to one benzene residue and the methyl radicle to the other. If all three substituting groups were attached to one benzene residue or a hydroxyl to one and the methyl radicle and a hydroxyl to the other, fusion with caustic alkali would certainly furnish either benzoic acid or one of its derivatives (Liebermann, *Ber.*, 1879, **12**, 1293). Moreover, the methyl radicle attached to one benzene residue and the quinol group present in the other afford to oxidising agents two points of attack, and furnish an explanation of the ease with which disruption of the molecule occurs. The only possible formulæ for chrysophanic acid are therefore



I.

or



II.

5 : 8-Dihydroxy-2-methylanthraquinone (formula II) has, however, been synthesised (Niementowski, *Ber.*, 1900, **33**, 1634), and appears to coincide in physical and chemical characters with chrysophanic acid. As it seemed likely that the possibility of the identity of the synthetical and natural products had been overlooked, we prepared some 5 : 8-dihydroxy-2-methylanthraquinone and found that it was not identical with chrysophanic acid. Formula II must therefore be abandoned, and we may regard I as the constitutional formula of chrysophanic acid, which is that previously suggested by Hesse (*loc. cit.*).

If this formula for chrysophanic acid is accepted, it necessarily follows that chrysarobin and dichrysarobin must be represented as follows: $[5:8](OH)_2C_6H_2<\begin{matrix}C(OH)\\ |\\ CH\end{matrix}>C_6H_3\cdot CH_3[1]$,

(Chrysarobin.)

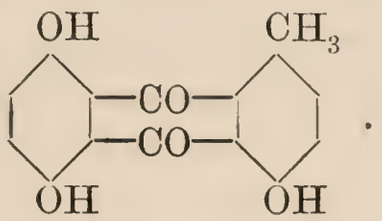
$$[5:8](OH)_2C_6H_2<\begin{matrix}C(OH)\\ |\\ CH\end{matrix}>C_6H_3\cdot CH_3[1] \qquad [5:8](OH)_2C_6H_2<\begin{matrix}C(OH)\\ |\\ CH\end{matrix}>C_6H_3\cdot CH_3[1]$$
$$\text{——————O——————}$$

(Dichrysarobin.)

We have endeavoured to synthesise 5 : 8-dihydroxy-1-methylanthraquinone by the condensation of hydroxysalicylic acid with *o*- and with *m*-toluic acids and of 1-methylphthalic anhydride with quinol, but in

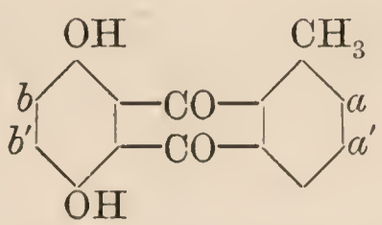
all cases without success. The failure in the latter case is inexplicable, as 2-methylphthalic anhydride readily condenses with quinol.

Hesse has also suggested the following formula for emodin :



This, however, is incorrect, as emodin yields a monomethyl ether, which would not be the case if the three hydroxyl groups occupied the positions indicated in the above formula. It follows that one hydroxyl group in emodin occupies the meta-position with regard to a carbonyl residue. There are three reasons why emodin should be regarded as a hydroxyl derivative of chrysophanic acid : (1) as both substances occur together in certain plants, notably rhubarb, it is most probable that both contain the same complex, and differ only by the presence of an additional hydroxyl group in emodin ; (2) both chrysophanic acid and emodin behave similarly when fused with caustic alkali or when oxidised with permanganate, neither yielding any derivative of benzoic acid ; (3) emodin, on distillation with zinc dust, yields a methyl anthracene, which is regarded by Liebermann as being the 2-methyl compound, whereas Perkin (Trans., 1894, **65**, 925) supposes it to be the 1-methyl derivative.

If it is admitted that emodin contains the chrysophanic acid residue, then the additional hydroxyl must occupy one of the following positions *a*, *a'*, *b*, or *b'* :

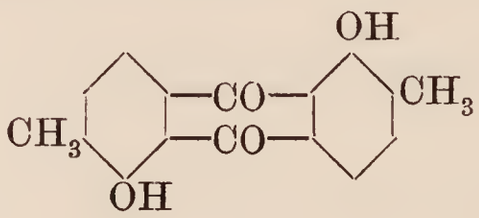


If the third hydroxyl in emodin occupied position *b* or *b'*, we should expect to find indications of dyeing properties, owing to the position of the two contiguous hydroxyl groups with respect to the carbonyl radicle. Emodin, however, has been shown to be quite devoid of these properties. It is therefore most probable that the additional hydroxyl group occupies position *a* or *a'*, and emodin would thus be represented by one of the following formulæ :

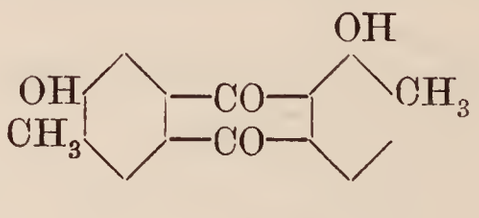
Emodin.

Inasmuch as the synthesis of emodin could alone serve to distinguish between these formulæ, we have made numerous attempts to accomplish this by the condensation of hydroxysalicylic acid with the different hydroxytoluic acids under varying conditions of temperature and by the use of different condensing agents, such as zinc chloride and phosphoric anhydride, in addition to sulphuric acid. The desired condensation, however, did not take place, and it would appear that the hydroxysalicylic acid is so readily oxidised that it undergoes decomposition before the temperature necessary for condensation is reached.

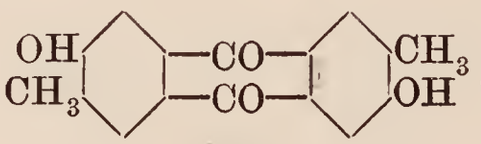
In attempting the condensation of hydroxysalicylic with hydroxy-*p*-toluic acid ($CH_3 : OH = 1 : 2$), it was found that a reaction had occurred, but the examination of the resulting products proved that they were formed by the condensation of two molecules of the hydroxy-*p*-toluic acid, and that the hydroxysalicylic acid took no part in the reaction. This was afterwards confirmed by the condensation of hydroxy-*p*-toluic acid alone. The formation of three, and only three, isomeric dihydroxydimethylanthraquinones by the condensation of two molecules of hydroxy-*p*-toluic acid is possible, and three isomerides have actually been isolated. The formulæ of the isomerides are as follows :



I.



II.



III.

The correct formulæ of the products were determined by the behaviour of these substances towards ammonia and methylating agents. On methylation, the substance denoted by formula III would yield a dimethyl ether, the compound No. II would furnish a monomethyl ether, whilst the isomeride indicated by I would remain unchanged. The pure substances have been isolated and characterised.

Experimental.

Emodin methyl ether, $C_6H_2(OH)_2\langle\begin{matrix}CO\\CO\end{matrix}\rangle C_6H_2(CH_3)(OCH_3)$.

This compound was prepared as follows: 2·7 parts of emodin, 4·5 parts of methyl iodide, and 0·7 part of sodium dissolved in methyl alcohol were heated together in a reflux apparatus at 60° for 24 hours, or in

a sealed tube at 100° for 2 to 3 hours. The alcoholic liquid, which had now lost its original red colour, deposited yellow crystals, and these, when recrystallised from hot alcohol, separated in fine, yellow needles melting at 200°, the melting point remaining unchanged on further crystallisation. The ether was insoluble in sodium carbonate solution, but dissolved in cold aqueous sodium hydroxide to a red solution.

0·0864 gave 0·2134 CO_2 and 0·0346 H_2O. C = 67·4 ; H = 4·4.
0·0782 „ by Zeisel's method, 0·0638 AgI. OCH_3 = 5·2.
*0·2206 „ „ „ 0·185 AgI. OCH_3 = 5·3.
$C_{16}H_{12}O_5$ requires C = 67·6 ; H = 4·2 ; OCH_3 = 5·3 per cent.

The *acetyl* compound, $C_{16}H_{10}O_5(C_2H_3O)_2$, prepared by the action of acetic anhydride and sodium acetate, was purified by recrystallisation from hot alcohol until its melting point was constant at 157°.

0·1406 gave 0·3364 CO_2 and 0·0576 H_2O. C = 65·2 ; H = 4·5.
$C_{20}H_{16}O_7$ requires C = 65·2 ; H = 4·3 per cent.

When emodin methyl ether was fused with potassium hydroxide, a small quantity of phenol was produced, together with a small amount of an acid which sublimed forming light green crystals which did not melt below 250°, and developed purple and red colorations with ferric chloride and sulphuric acid respectively. Unfortunately, the quantity of this acid produced was too small to admit of further examination. It would appear that this emodin methyl ether is not identical with that obtained by Perkin and Hummel from *Ventilago madrasapatana* (Trans., 1894, **65**, 932), since the acetyl compound of the latter melted at 185°, and the ether yielded crystalline mono- and tetra-nitro-compounds.

Under similar conditions, the ether prepared from emodin afforded no definite compound with nitric acid.

3 : 5-*Dihydroxy*-2 : 6-*dimethylanthraquinone*, $C_{16}H_{12}O_4$.

This was produced during an attempt to condense hydroxysalicylic with hydroxy-*p*-toluic acid (CH_3 : OH = 1 : 2), but it was afterwards found that the former acid took no part in the condensation. *m*-Hydroxy-*p*-toluic acid, either alone or mixed with an equal part of hydroxysalicylic acid, was heated in an oil-bath at 110° to 140° for from 7 to 10 hours with ten parts of concentrated sulphuric acid. Whilst still warm, the deep red liquid was poured into ten volumes of water and allowed to cool. The dirty green precipitate produced was thoroughly washed with water, dried, and then extracted with benzene in a Soxhlet's apparatus. After removing the benzene by distillation, the

* This specimen was obtained by the reaction at 100° in a sealed tube.

residue was dissolved in a large volume of hot glacial acetic acid, the solution being boiled with animal charcoal. The crystals, which separated on cooling from the filtered solution, did not melt below 300°; they were crystallised twice from ethyl acetate and thus obtained as bright golden-yellow leaflets. The substance dissolved in concentrated sulphuric acid to a deep pink solution, and developed a brownish-red coloration in ammonia, a full red tint being produced in aqueous caustic alkalis; it is only slightly soluble in aqueous sodium carbonate, forming a reddish-yellow solution.

0·0854 gave 0·2224 CO_2 and 0·0344 H_2O. C = 71·0; H = 4·5.
0·1164 „ 0·3030 CO_2 „ 0·0504 H_2O. C = 71·0; H = 4·8.
$C_{16}H_{12}O_4$ requires C = 71·6; H = 4·5 per cent.

The *acetyl* compound, $C_{16}H_{10}O_4(C_2H_3O)_2$, prepared by the action of acetic anhydride and sodium acetate, formed long, yellow, acicular crystals melting at 215°, and this melting point was not altered on recrystallisation.

0·0842 gave 0·2102 CO_2 and 0·0372 H_2O. C = 68·1; H = 4·8.
$C_{20}H_{16}O_6$ requires C = 68·1; H = 4·5 per cent.

The *monomethyl ether*, $C_{16}H_{11}O_4(CH_3)$, was formed by heating the dihydroxydimethylanthraquinone at 100° for 2 hours in a sealed tube with equivalent amounts of sodium and methyl iodide dissolved in methyl alcohol. The product, which separated on cooling, was collected, washed with water, and repeatedly crystallised from hot ethyl acetate, the ether being thus obtained in golden-yellow, acicular crystals melting at 214—215°.

0·093 gave, by Zeisel's method, 0·0702 AgI. OCH_3 = 4·8.
$C_{17}H_{14}O_4$ requires OCH_3 = 5·3 per cent.

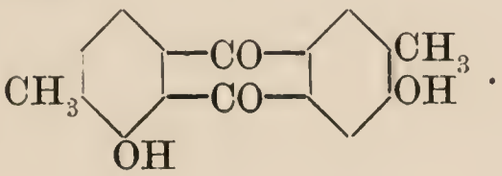
A dimethyl ether could not be obtained.

The *acetyl* compound, $C_{16}H_{10}O_4(CH_3)(C_2H_3O)$, prepared in the usual way with acetic anhydride and sodium acetate, when crystallised from absolute alcohol, formed light yellow, acicular crystals melting at 195—196°.

0·1012 gave 0·2580 CO_2 and 0·0440 H_2O. C = 69·5; H = 4·8.
0·0946 „ 0·2412 CO_2 „ 0·0428 H_2O. C = 69·5; H = 5·0.
$C_{19}H_{16}O_5$ requires C = 70·3; H = 4·9 per cent.

The formation of the monomethyl ether proves that the condensation product contains only one hydroxyl group contiguous to th carbonyl, and as of the three isomerides possible by the condensation of two molecules of *m*-hydroxy-*p*-toluic acid only one fulfils this con

dition, it follows that the substance just described must be represented by the following formula :

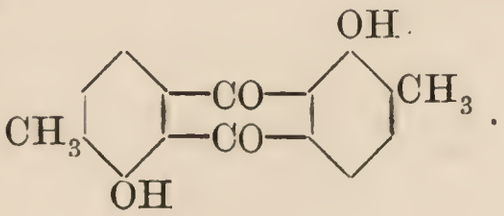


1 : 5-*Dihydroxy*-2 : 6-*dimethylanthraquinone*, $C_{16}H_{12}O_4$.

This substance is formed together with the isomeric 3 : 5-dihydroxy-2 : 6-dimethylanthraquinone under the conditions previously described (p. 1331). It is, however, only produced in very small quantity, and we have not obtained it by the condensation of hydroxy-*p*-toluic acid alone. It was isolated from the mother liquors, from which its isomeride had separated, by adding water to the glacial acetic acid solution. The product was purified by dissolving in hot chloroform, in which the yellow isomeride is almost insoluble, and precipitating from the chloroform solution by the cautious addition of methyl alcohol. After repeated crystallisation from chloroform and petroleum ether, the compound was obtained in scarlet, acicular crystals melting at 224—225°.

0·0732 gave 0·191 CO_2 and 0·0298 H_2O. C = 71·2 ; H = 4·5.
$C_{16}H_{12}O_4$ requires C = 71·6 ; H = 4·5 per cent.

The crystals were insoluble in ammonia or sodium carbonate solution, but dissolved in concentrated sulphuric acid to a purple solution, and developed a pink coloration with aqueous caustic alkalis. The substance remained unchanged when heated with excess of methyl iodide and sodium in methyl alcohol at 100° in a sealed tube. The insolubility of this isomeride in ammonia and its inertness towards methylating agents prove that both hydroxyl groups must be contiguous to carbonyl, and the compound must therefore be represented by the following formula :



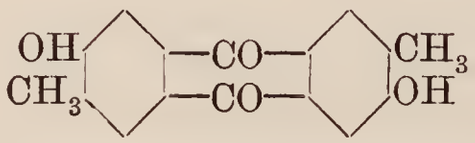
3 : 7-*Dihydroxy*-2 : 6-*dimethylanthraquinone*, $C_{16}H_{12}O_4$.

This substance is formed in very small proportion together with the isomeric 3 : 5-dihydroxy-2 : 6-dimethylanthraquinone by the condensation of two molecules of *m*-hydroxy-*p*-toluic acid ; it was separated from the glacial acetic acid mother liquors by precipitation with water

and crystallised repeatedly from absolute alcohol until of constant melting point. It then formed fine, orange-yellow, acicular crystals melting at 232°, was readily soluble in ammonia to a red solution, and developed a reddish-purple coloration in concentrated sulphuric acid.

0·0486 gave 0·1264 CO_2 and 0·021 H_2O. C = 71·0; H = 4·8.
$C_{16}H_{12}O_4$ requires C = 71·6; H = 4·5 per cent.

Although sufficient material was not available for any further experiments, yet the ready solubility of the substance in ammonia and its distinctive character leave no doubt but that this substance is the third possible isomeride, and therefore by exclusion has the following formula :



Emodin was fused with caustic alkali and oxidised with potassium permanganate under varying conditions, but in no case could any definite product be isolated.

An attempt to prepare a methyl ether of 5 : 8-dihydroxy-2-methylanthraquinone was unsuccessful. Further proof is thus afforded of the correctness of the generalisation that in derivatives of anthraquinone under the conditions mentioned, only those hydroxyl groups are capable of methylation which are not contiguous to either of the two carbonyl groups.

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